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Health Effects Assessment for 2,4- and 2,6-Dinitrotoluene

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR 2,4- AND 2,6-DINITROTOLUENE

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 2,4- and 2,6-dinitrotoluene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to June, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Dinitrotoluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-045. NTIS PB81-117566.

U.S. EPA. 1983a. Reportable Quantity Document for Benzene, 1-Methyl-2,4-Dinitro (2,4-Dinitrotoluene). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for Benzene, 1-Methyl-2,6-Dinitro (2,6-Dinitrotoluene). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1986a. Health and Environmental Effects Profile for Dinitrotoluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data was limited in scope, which tended to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

2,4-Dinitrotoluene has been demonstrated to be carcinogenic in rats and mice when fed in the diet (Ellis et al., 1979; Lee et al., 1978) as has technical grade dinitrotoluene (CIIT, 1982), composed of ~76% 2,4-, ~19% 2,6- and smaller amounts of other isomers of dinitrotoluene. U.S. EPA (1980a, 1986a) derived several q_1^*s based on the occurrence of liver or liver and mammary tumors in rats and mice from these studies. A human q_1^* of 0.683 $(mg/kg/day)^{-1}$ based on the incidence of liver and mammary tumors in female rats (Ellis et al., 1979; U.S. EPA, 1986a) was selected as the most stringent estimate of the carcinogenicity of 2,4-dinitrotoluene to humans.

Data were presented suggesting that the 2,6-isomer may be more a potent oral carcinogen than the 2,4-isomer. The data were sufficient for weight of evidence classification but inadequate for quantitative risk analysis.

Data were not located regarding the inhalation toxicity of the dinitrotoluenes.

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LIST OF ABBREVIATIONS

bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
FSH	Follicle stimulating hormone
GGT+	γ-Glutamyl transpeptidase positive
K_{oc}	Soil sorption coefficient standardized with respect to soil organic matter
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PEL	Permissible exposure level
ppm	Parts per million
q_1^*	Cancer potency slope
RfD	Reference dose
RfD_S	Subchronic reference dose
STEL	Short-term exposed level
TLV	Threshold limit value
TWA	Time-weighted average

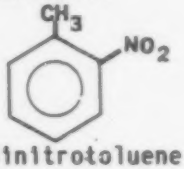
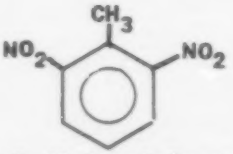
1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties of 2,4-dinitrotoluene (CAS No. 121-14-2) and 2,6-dinitrotoluene (CAS No. 606-20-2) are presented in Table 1-1. Synonyms for dinitrotoluene are methyldinitrobenzene, dinitrophenylmethane and DNT. Synonyms for 2,4-dinitrotoluene are 1-methyl-2,4-dinitrobenzene, o,p-dinitrotoluene and 2,4-DNT. Synonyms for 2,6-dinitrotoluene are 2-methyl-1,3-dinitrobenzene and 2,6-DNT.

The atmospheric half-lives listed for 2,4- and 2,6-dinitrotoluene are based on the estimated rate constant of 3×10^{-11} cm^3 $molecule^{-1}$ sec^{-1} for the reaction of the dinitrotoluene isomers with photochemically generated OH radical (OH radical concentration of 8×10^5 molecules/cm^3) (U.S. EPA, 1986b). The half-life of 2,4-dinitrotoluene in water was based on an investigation of the contaminants in the Rhine River (Zoeteman et al., 1980) and laboratory studies using Waconda Bay Water (Spanggord et al., 1980). 2,6-Dinitrotoluene is expected to have a half-life similar to that of 2,4-dinitrotoluene. Photochemical degradation should be an important removal mechanism, considering estimated photolysis half-lives range from 12 minutes for 2,6-dinitrotoluene in river water to 2.7, 3.7 and 9.6 hours for 2,4-dinitrotoluene in river, pond and bay water, respectively (Spanggord et al., 1980; Zepp et al., 1984). Biodegradation has also been observed to be a relatively rapid transformation process during some screening studies (Davis et al., 1981; Spanggord et al., 1980). 2,4-Dinitrotoluene and 2,6-dinitrotoluene could potentially adsorb to humus and clay particulate matter and sediments since polynitroaromatic compounds have the ability to form very stable charge-transfer complexes with more highly electronegative aromatic compounds (Callahan et al., 1979).

TABLE 1-1

Selected Physical and Chemical Properties and Half-lives
for 2,4- and 2,6-Dinitrotoluene

Property	Value	Reference
Chemical class:	nitroaromatic	
Chemical formula:	 2,4-dinitrotoluene	 2,6-dinitrotoluene
Molecular weight:	182.14	
Melting point:	300°C (slight decomposition) for 2,4-DNT; NA for 2,6-DNT	Verschueren, 1983
Boiling point:	67-70°C for 2,4-DNT 64-66°C for 2,6-DNT	Aldrich, 1984 Verschueren, 1983
Vapor pressure:	2,4-: 1.1×10^{-4} mm Hg at 20°C (extrapolated)	Spanggord et al., 1980
	2,6-: 2.87×10^{-4} mm Hg at 20°C	Pella, 1977
Water solubility:	2,4-: 300 mg/ℓ at 22°C 2,6-: NA	Dunlap, 1981
Log octanol/water partition coefficient:	2,4-: 1.98	Hansch and Leo, 1985
	2,6-: 1.76 (estimated)	U.S. EPA, 1986c
Bioconcentration factor:	2,4-: 19-25 (estimated) 2,6-: 13 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	2,4-: 190-285 (estimated) 2,6-: 216 (estimated)	Lyman et al., 1982
Half-lives in air:	2,4- and 2,6-: 8.0 hours (estimated)	U.S. EPA, 1986b
water:	2,4-: 1.7 days	Zoeteman et al., 1980

NA = Not available

Information regarding the persistence of 2,4- and 2,6-dinitritoluene in soil could not be located in the available literature. Biodegradation of 2,4- and 2,6-dinitrotoluene under aerobic and anaerobic conditions in water suggests that these compounds may undergo microbial decomposition in soil.

The estimated K_{oc} values of the dinitrotoluenes indicate that some leaching may occur, but that chemical binding with humus and clay components of soil may reduce the probability of leaching (Callahan et al., 1979).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Hodgson et al. (1977) reported that 60-90% of a dose of ^{14}C-ring labelled dinitrotoluenes was absorbed within 24 hours of oral administration in rats. The 2,4-isomer was absorbed more readily than the 2,6-isomer. U.S. EPA (1981) stated that, based upon urinary and fecal excretion findings, only 8-12% of an administered oral dose of [^{14}C]-2,4-dinitrotoluene was absorbed in mice, but that 75-85% of the dose was absorbed in rats, rabbits, dogs and monkeys.

Mori et al. (1978) observed peak levels of radioactivity in the blood of male rats at 6 hours after a single oral 22.2 mg/kg dose of ^{3}H-2,4-dinitrotoluene.

2.2. INHALATION

Turner (1986) analyzed urine samples from workers exposed to mixed isomers of dinitrotoluene, and found that urinary excretion of metabolites of dinitrotoluenes increased during the workday and declined to nearly undetectable levels by the start of the next workday. These data suggest that rapid absorption of dinitrotoluenes occurs following inhalation, but no conclusions can be drawn regarding the proportion of inhaled material absorbed.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Ellis et al. (1985) treated male and female beagle dogs with 1, 5 or 25 mg/kg/day 2,4-dinitrotoluene in gelatin capsules for 4 or 13 weeks before sacrifice. At 5 and 25 mg/kg/day, the intensity of neurotoxicity, ranging from incoordination and stiffness to total limb paralysis, was directly related to both dose and duration of exposure. Hematological changes (methemoglobinemia, compensatory anemia) and testicular degeneration were observed in the 25 mg/kg/day dogs. As part of a chronic study, Ellis et al. (1985) found neuropathy and anemia in dogs treated for 13 weeks with 10 mg/kg/day 2,4-dinitrotoluene. During this 13-week period, no dog given 0.2 or 1.5 mg/kg/day was apparently affected; the dose of 1.5 mg/kg/day can therefore be considered a NOEL for subchronic oral exposure to 2,4-dinitrotoluene.

Twenty-six week dietary studies using rats that were fed with mixed-isomer dinitrotoluene, revealed methemoglobinemia, anemia, myocarditis, extramedullary hematopoiesis, bile duct necrosis and testicular degeneration at 35 mg/kg/day (CIIT, 1982). Effects at 14 mg/kg/day were restricted to increases in hepatic weights, leukocytosis, corneal aberrations and yellow hepatic foci; 3.5 mg/kg caused a statistically significant decrease in body weight gain.

Hong et al. (1985) found that dietary administration of 2,4-dinitrotoluene (0.2%) for 13 weeks caused inhibitions in weight gain and hepatocellular dysplasia in male mice, whereas 0.7% was associated with mortality. Several other subchronic studies in rats (Lee et al., 1985; NCI, 1978; Kozuka et al., 1979) and mice (NCI, 1978) either reported effect levels at doses considerably higher than those used by Ellis et al. (1985) and CIIT

(1982), or do not describe their results in adequate detail for reliable evaluation and interpretation.

In the only available study of the subchronic oral toxicity of pure 2,6-dinitrotoluene (Ellis et al., 1976), dogs were treated for 13 weeks at 4, 20 or 100 mg/kg/day in gelatin capsules, and rats and mice were fed dietary levels of 0.01, 0.05 or 0.25%. This isomer produced effects similar to those of 2,4-dinitrotoluene. These effects included decreased muscular coordination, weight loss, methemoglobinemia, anemia, and splenic, CNS and testicular damage. A subchronic NOAEL for 2,6-dinitrotoluene was not defined in this experiment.

3.1.2. Inhalation. Pertinent data regarding the subchronic inhalation toxicity of 2,4- or 2,6-dinitrotoluene could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. The CIIT (1982) administered technical grade dinitrotoluene (consisting of a mixture of isomers) to rats of both sexes in feed at dietary concentrations that provided doses of 3.5, 14.0 and 35.0 mg/kg bw/day for 78 weeks. Rats at the high concentration were sacrificed at week 55 in extremis. A statistically significant and dose-related depression in rate of body weight gain was noted in all treated groups during the first 52 weeks of the experiment. Hematological data suggested that a low grade regenerative anemia occurred in high-dose males and females. Treatment-related elevated relative liver and brain weight in all treated rats and elevated relative kidney weights in all but the low-dose males were consistently observed. Gross necropsy revealed white or yellow foci in the livers of all treated rats. At termination, histopathological evidence of hepatotoxicity, chronic interstitial nephritis and parathyroid hyperplasia were observed in all treated groups.

In another chronic rat study, diets containing 0, 0.0015, 0.01 and 0.07% 2,4-dinitrotoluene were administered to groups of 38 males and 38 females (Ellis et al., 1979; Lee et al., 1985). After 12 months, eight males and eight females from each group were killed and examined, while the remaining surviving rats were sacrificed after 24 months. Weight gain in high-dose animals was markedly reduced, reaching a plateau after 2 months in females and 4 months in males. Growth in middle-dose males and females began to decrease during month 9, while low-dose rats had growth rates comparable with controls. Anemia, partially compensated as evidenced by increased reticulocyte counts, was prominent in middle- and high-dose males and high-dose females after 12 months. Cumulative deaths for high-dose males and females were significantly higher than in controls; 50% mortality occurred in high-dose rats by about month 20 and in controls by about month 23. The most striking lesion was the progressive development of hyperplastic foci in the liver, the severity of which was dose-dependent. These alterations were observed in all male treatment groups and in high-dose females. Neoplastic nodules were also present in the majority of high-dose males and females. Hemosiderosis of the spleen occurred in a majority of high-dose rats.

Similar hepatic changes were found in dogs treated with capsules containing 1.5 or 10 mg/kg/day 2,4-dinitrotoluene for 104-108 weeks (Ellis et al., 1985). Dogs were more susceptible to neurotoxic effects than were rats. An intake of 0.2 mg/kg/day had no effect. The investigators found compensatory anemia at the high concentration.

Toxicity data from Hong et al. (1985) for 2,4-dinitrotoluene failed to define chronic thresholds in mice because mice appear to be less susceptible than rats and experiments in mice used higher dietary concentrations. In a chronic experiment using rats and mice, the NCI (1978) observed treatment-related inhibition of body weight gain in both species, but no evidence of

histopathological changes. These studies are of little value in assessment of chronic toxicity risk because adverse effects were observed at 80 ppm in the diet, the lowest dietary concentration tested.

Pertinent data regarding the chronic oral toxicity of 2,6-dinitrotoluene could not be located in the available literature.

3.2.2. Inhalation. McGee et al. (1942) observed that workers exposed to unspecified levels of 2,4-dinitrotoluene experienced an unpleasant metallic taste, headache, muscular weakness, dizziness, pallor, cyanosis and anemia.

There were no additional data in the available literature on the toxic effects of dinitrotoluene isomers after chronic inhalation exposure, except for occupational studies which measured the effects of exposure upon reproductive performance (Section 3.3.2.).

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. F344 rat dams administered 14-150 mg/kg/day technical grade dinitrotoluene on gestation days 7-20 had no significant differences from controls in the numbers of resorptions, or dead or live fetuses (Price et al., 1985). At 150 mg/kg/day, there was a 3-fold increase, over control values, in prenatal mortality. At 100 mg/kg/day, fetuses had significantly decreased reticulocyte and red cell counts. Mortality in the dams was increased at the high dose. Related studies (Ellis et al., 1979; Smith, 1983) indicated the absence of fetal effects below levels that produced maternal toxicity.

In chronic dietary studies with 2,4-dinitrotoluene, decreases in spermatogenesis, testicular atrophy, degeneration of the seminiferous tubules and deficiencies in oogenesis were found in rats at 0.57 mg/kg bw/day (Lee et al., 1985), in mice at 14 mg/kg bw/day (Hong et al., 1985) and in dogs at 25 mg/kg bw/day (Ellis et al., 1985). In a 3-generation rat study, however,

Ellis et al. (1979) found that dietary intakes of 0.57-45 mg/kg bw/day, in both males and females, had no treatment-related effects on any indices of reproduction, in spite of the histological evidence of adverse effects on germ cell production in males.

Pertinent data regarding the reproductive effects of oral exposure to 2,6-dinitrotoluene could not be located in the available literature.

3.3.2. Inhalation. Ahrenholz (1980) studied the reproductive effects of exposure to mixed isomers of dinitrotoluene in male workers in a toluene-diamine plant. Measured exposure levels were 0-0.10 mg/m³. There was a slight, not statistically significant increase in the number of spontaneous abortions in the wives of dinitrotoluene-exposed workers and a significant reduction in the sperm count of exposed workers, relative to controls. The sperm count of the control (nonexposed) group, however, was abnormally high, obscuring the significance of the results.

Hamill et al. (1982) studied the effects of exposure to concentrations of dinitrotoluene and toluene diamine that were within the limits of unspecified OSHA standards. In 119 controls and 84 exposed workers, there were no effects on measures of reproductive performance, including sperm counts and morphology, serum FSH, testicular volume, and complete urogenital examination.

3.4. TOXICANT INTERACTIONS

Alcohol ingestion has a synergistic effect on the toxicity of 2,4-dinitrotoluene (U.S. EPA, 1980a). Exposed workers who drank alcohol shortly after a workshift experienced substernal pressure, precardial palpitation, fullness of the head, and severe acute illness. U.S. EPA (1980a) noted that alcohol ingestion usually increases susceptibility to cyanosis associated with 2,4-dinitrotoluene.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenic effects in humans of oral or inhalation exposure to 2,4- or 2,6-dinitrotoluene could not be located in the available literature.

4.2. BIOASSAY

4.2.1. Oral. Several long-term dietary cancer bioassays with relatively pure 2,4-dinitrotoluene and a technical grade mixture of dinitrotoluenes have been performed and were recently reviewed by U.S. EPA (1986a). Because of the time and budgetary constraints of this task, only salient data pertaining to the issue of the carcinogenicity of the dinitrotoluene isomers will be presented.

NCI (1978) performed a cancer bioassay using rats and mice of both sexes with practical grade 2,4-dinitrotoluene of ~95% purity. The nature of the impurities was not reported. Rats received diets containing 0, 80 or 200 ppm and mice received diets containing 0, 80 or 400 ppm. Test diets were fed for 78 weeks and untreated diets were fed for an additional 26 weeks to rats and 13 weeks to mice before termination. Survival did not appear to be affected by treatment. Although neither species had a significantly increased incidence of malignant tumors, male rats in both treated groups had an increased incidence of benign subcutaneous fibromas and high-dose female rats had an increased incidence of benign mammary fibroadenomas.

In another study with technical grade 2,4-dinitrotoluene, diets containing 0, 0.0015, 0.01 or 0.07% were fed to rats for 24 months (Lee et al., 1978; Ellis et al., 1979). The only statistically significant increase of tumor incidence was in the occurrence of hepatocellular carcinomas alone or combined with neoplastic nodules and the occurrence of benign tumors in the

mammary gland alone or combined with malignant tumors, both tumor types in female rats. Although shortened lifespans were observed in middle- and high-dose rats of both sexes, mortality did not appear to affect the expression of the carcinogenicity of the test chemical, which was judged to be weak (U.S EPA, 1986a).

Ellis et al. (1979) fed diets containing technical grade 2,4-dinitrotoluene at 0, 100, 700 or 5000 ppm to mice for 24 months. Mortality in the high-dose mice precluded their inclusion in the data analysis. The most noteworthy observation was an increased incidence of kidney tumors in 700 ppm male mice.

An extensive study using rats by CIIT (1982) contrasts the oncogenicity of the purified 2,4-isomer with that of technical grade dinitrotoluene. Technical grade dinitrotoluene was fed in the diets to rats to provide daily dosages of 0, 3.5, 14.0 or 35.0 mg/kg/day for up to 104 weeks. The technical grade material used consisted of 76.4% 2,4-, 18.8% 2,6- and smaller amounts of the other isomers of dinitrotoluene. The carcinogenic potential of the technical material appeared to be much greater than that of 2,4-dinitrotoluene alone. Malignant tumors that included a high incidence of hepatocellular carcinomas and a few cholangiocarcinomas (considered to be rare in rats) were noted in 100% of high-dose male and female rats that survived $\geq$12 months.

The greater oncogenic potential of the technical material compared with relatively pure 2,4-dinitrotoluene was attributed by Popp and Leonard (1982) to the greater oncogenicity of the 2,6-isomer. These investigators observed that 100% of all rats fed 14 mg/kg/day, and 95% fed 7 mg/kg/day of >99.9% pure 2,6-dinitrotoluene developed hepatocellular carcinomas within 1 year.

In contrast, 27 mg/kg/day >99.9% pure 2,4-dinitrotoluene induced no hepatic neoplasia after a comparable 1-year period. Actual incidence data were not provided. In conjunction with results from initiation-promotion studies (Section 4.3.), these data suggest that the 2,6-isomer is the more potent hepatocarcinogen.

4.2.2. Inhalation. Pertinent data regarding the induction of cancer in experimental animals after inhalation exposure to dinitrotoluene could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Popp and Leonard (1982) tested 2,4-, 2,6- and technical grade dinitrotoluene as initiators in a short-term assay in which rats were treated with the test chemical orally and subjected to partial hepatectomy 12 hours later. The presence of GGT+ foci in the liver, suggestive of initiating activity, was observed only for 2,6-dinitrotoluene and the technical product. In a promotion experiment (Popp and Leonard, 1982), positive results (increased GGT+ foci) were observed for both the 2,4- and 2,6-isomers, with the 2,6-isomer yielding the stronger response. The experiment was conducted in rats initiated with a single intraperitoneal injection of diethylnitrosamine; the test chemicals were fed in the diet for 12 weeks. These studies suggest that only the 2,6-isomer has detectable initiating activity, but that both 2,4- and 2,6-dinitrotoluene may act as promotors, with the 2,6-isomer having the greater potency.

In a two-stage skin-painting study using mice, 2,6- but not 2,4-dinitrotoluene given as initiators followed by promotion with tetradecanoyl phorbate acetate increased the incidence of squamous cell carcinomas, although the result was not statistically significant.

Neither 2,4- nor 2,6-dinitrotoluene induced increases in lung tumors in Strain A mice (Slaga et al., 1985; Stoner et al., 1984; Schut et al., 1982).

The genotoxicity of the various dinitrotoluene isomers has been studied extensively, and was recently reviewed by U.S. EPA (1986a). Both 2,4- and 2,6-dinitrotoluene were slightly mutagenic in Salmonella typhimurium strain TA98 (Couch et al., 1981). Other studies indicated that these isomers induced frameshift mutations in S. typhimurium strains TA1536, TA1537 and TA1538 (Tokiwa et al., 1981).

Neither isomer caused unscheduled DNA synthesis in vitro in primary rat hepatocytes (Bermudez et al., 1979), although a single dose of technical grade dinitrotoluene in male rats induced significant repair activity in vivo (Mirsalis and Butterworth, 1982). Pure 2,4-dinitrotoluene was ineffective in the whole animal assay and the induced repair activity was attributed by the authors (Mirsalis and Butterworth, 1982) to the 2,6-isomer. At high doses, both 2,4- and 2,6-dinitrotoluene have been found to cause chromatid breaks in kidney cells and lymphocytes from rats (Lee et al., 1978). Dominant lethal assays in male rats and mice have revealed equivocal, but generally negative results (Ellis et al., 1979; Borzelleca and Carchman, 1982).

4.4. WEIGHT OF EVIDENCE

Based upon positive data for oncogenicity from bioassays in both rats and mice (Ellis et al., 1979), and in the absence of appropriate human data, 2,4-dinitrotoluene can be classified an IARC Group 2B carcinogen; that is, this chemical is probably carcinogenic in humans, based upon experimental animal studies. According to U.S. EPA (1986d) guidelines, 2,4-dinitrotoluene would also be classified as an EPA Group B2 carcinogen because of the existence of sufficient evidence of carcinogenicity in two species of

animals (Ellis et al., 1979). It should be noted, however, that the effects of the oncogenic potential of 2,6-dinitrotoluene (as a minor contaminant) on the carcinogenicity of the practical grade 2,4-dinitrotoluene used in these experiments is unclear.

The results of Popp and Leonard (1982) and CIIT (1982) clearly establish the carcinogenicity of 2,6-dinitrotoluene in animals, resulting in an IARC classification in Group 2B, or EPA Group B2.

5. REGULATORY STANDARDS AND CRITERIA

Based upon a human consumption of 2 ℓ of water and 6.5 g of fish and shellfish daily, the U.S. EPA (1980a) determined ambient water quality criteria for 2,4-dinitrotoluene of 1.1, 0.11 and 0.011 µg/ℓ, based on excess cancer risks of 10^{-5}, 10^{-6} and 10^{-7}, respectively. These criteria were based on increased incidences of liver and mammary tumors in rats fed 2,4-dinitrotoluene in the diet for 24 months (Lee et al., 1978).

ACGIH (1985) adopted a TLV-TWA for commercial dinitrotoluene of 1.5 mg/m³, accompanied by a "skin" designation for hazards from dermal absorption, and deleted the TLV-STEL of 5 mg/m³. ACGIH (1986) reported that the TLV-TWA was derived by analogy to nitro and dinitrobenzenes. ACGIH (1986) based the values for each compound upon earlier work indicating that methemoglobinemia was the first toxic symptom observed. The OSHA (1985) PEL for dinitrotoluene (not otherwise specified) is also 1.5 mg/m³.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Both 2,4- and 2,6-dinitrotoluene have been shown to be carcinogenic in experimental animals by the oral route, and data are sufficient for derivation of a q_1^* for the 2,4-isomer only. Calculation of an RfD_{SO} or RfD_{SI} is therefore inappropriate for these compounds.

6.2. REFERENCE DOSE (RfD)

Both 2,4- and 2,6-dinitrotoluene have been shown to be carcinogenic in experimental animals by the oral route, and data are sufficient for derivation of a q_1^* for the 2,4-isomer only. Calculation of an RfD_O or RfD_I is therefore inappropriate for these compounds.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The chronic bioassays most relevant for assessment of the oral carcinogenic potency of 2,4-dinitrotoluene were performed in rats and mice by Ellis et al. (1979). When animal results were analyzed individually (U.S. EPA, 1986a), the incidences of combined mammary/hepatic tumors in female rats was strongly concentration-related (Table 6-1). The U.S. EPA (1986a) observed differences in average body weight among the various groups of female rats, and converted rat doses (mg/kg/day) to comparable human doses by multiplying each rat dose by the cube root of the ratio of human body weight (70 kg) to rat body weight, within each dietary group. The human q_1^*, based upon the computerized model of Howe and Crump (1982), is 0.683 $(mg/kg/day)^{-1}$

The U.S. EPA (1980a, 1982) used the incidence of combined liver and mammary tumors in female rats in the 2-year study by Lee et al. (1978) as the basis for their q_1^* of 0.31 $(mg/kg/day)^{-1}$ (Table 6-2). Although the Lee et al. (1978) study was apparently the same as the Ellis et al. (1979)

TABLE 6-1

Cancer Data Sheet for Derivation of q_1^*
in Female Sprague-Dawley Rats

Compound: 2,4-dinitrotoluene

Reference: Ellis et al., 1979; U.S. EPA, 1986a

Species, strain, sex: rat, Sprague-Dawley, female

Body weight: 0.425 kg control; 0.425 kg low dose; 0.410 kg middle dose; 0.325 kg high dose (measured)

Length of exposure (le) = 24 months

Length of experiment (Le) = 24 months

Lifespan of animal (L) = 24 months

Tumor site and type: liver - hepatocellular carcinoma, neoplastic nodule; mammary gland - adenoma, fibroadenoma, fibroma, adenocarcinoma/carcinoma

Route/vehicle: oral, diet

Experimental Doses or Exposures		Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
(ppm)	(mg/kg/day)		
0	0	0	11/23
15	0.706	0.129	12/35
100	0.514	0.927	17/27
700	45.3	7.557	34/35

Unadjusted q_1^* from study = not calculated (see text)

Human $q_1^* = 0.68\ (mg/kg/day)^{-1}$

TABLE 6-2

Cancer Data Sheet for Derivation of q_1^* in Female CD Rats

Compound: practical-grade 2,4-dinitrotoluene

Reference: Lee et al., 1978; U.S. EPA, 1980a

Species, strain, sex: rat, CD, female

Body weight: 0.464 kg

Length of exposure (le) = 720 days

Length of experiment (Le) = 750 days

Lifespan of animal (L) = 750 days

Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested
0.0	11/31
0.75	13/43
5.0	18/35
35.0	35/43

Human q_1^* = 0.31 $(mg/kg/day)^{-1}$

study, the tumor incidence data used by the U.S. EPA (1980a) were not the same as those of Ellis et al. (1979), probably because the Lee et al. (1978) version was a preliminary report. In a later published version of this study (Lee et al., 1985), still another set of hepatic/mammary tumor data was presented. Because the incidence data of the Ellis et al. (1979) study were the most clearly presented, it is appropriate to adopt the current q_1^* of 0.683 $(mg/kg/day)^{-1}$ derived by U.S. EPA (1986a) as appropriately representing the carcinogenic potency of 2,4-dinitrotoluene based on experiments in rats.

The chronic mouse bioassay (Ellis et al., 1979) can also be used for carcinogenic risk assessment. Since most high concentration males died within 1 year, data are restricted to the controls and two lower dose dietary groups. A human q_1^* of 0.391 $(mg/kg/day)^{-1}$ was derived by the U.S. EPA (1986a) based on the occurrence of total kidney tumors in male rats (Table 6-3).

Because the q_1^* of 0.683 $(mg/kg/day)^{-1}$ (U.S. EPA, 1986a) based upon the rat data of Ellis et al. (1979) is higher and represents the more conservative evaluation of the carcinogenic risk of 2,4-dinitrotoluene to humans, it is adopted as the most appropriate estimate of carcinogenic risk for the purposes of this document (see Appendix).

The U.S. EPA (1986a) also derived human q_1^*s of 0.23 and 0.21 $(mg/kg/day)^{-1}$ for technical grade dinitrotoluene based on the incidence of liver tumors in male (Table 6-4) and female (Table 6-5) rats in the CIIT (1982) study. Data sufficient for derivation of an oral q_1^* for 2,6-dinitrotoluene were not available, although this isomer appears to be the more potent carcinogen.

TABLE 6-3

Cancer Data Sheet for Derivation of q_1^* in Male Swiss Mice

Compound: 2,4-dinitrotoluene

Reference: Ellis et al., 1979; U.S. EPA, 1986a

Species, strain, sex: mouse, Swiss, male

Body weight: 0.04 kg (measured)

Length of exposure (le) = 24 months

Length of experiment (Le) = 24 months

Lifespan of animal (L) = 24 months

Tumor site and type: kidney; cystic papillary adenoma, cystic papillary carcinoma, solid renal cell carcinoma

Route/vehicle: oral, diet

Experimental Doses or Exposures (ppm)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	0/20
100	13.3	4/21
700	96.9	16/17

Unadjusted q_1^* from study = 3.2×10^{-2} $(mg/kg/day)^{-1}$

Human q_1^* = 0.39 $(mg/kg/day)^{-1}$

TABLE 6-4

Cancer Data Sheet for Derivation of q_1^* in Male F344 Rats

Compound: technical-grade dinitrotoluene

Reference: CIIT, 1982

Species, strain, sex: rat, F344, male

Body weight: 0.37 kg control; 0.35 kg low dose; 0.29 kg high dose; (measured)

Length of exposure (le) = 104 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: liver; hepatocellular carcinoma, neoplastic nodule

Route/vehicle: oral, diet

Experimental Doses or Exposures (mg/kg/day)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	10/61
3.388	0.579	19/70
13.451	2.160	23/23

Unadjusted q_1^* from study = not calculated (see text)

Human $q_1^* = 0.23\ (mg/kg/day)^{-1}$

TABLE 6-5

Cancer Data Sheet for Derivation of q_1^* in Female F344 Rats

Compound: technical-grade dinitrotoluene

Reference: CIIT, 1982

Species, strain, sex: rat, F344, female

Body weight: 0.26 kg control; 0.24 kg low dose; 0.1$ kg high dose; (measured)

Length of exposure (le) = 104 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: liver; hepatocellular carcinoma, neoplastic nodule

Route/vehicle: oral, diet

Experimental Doses or Exposures (mg/kg/day)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	5/57
3.379	0.510	12/61
13.633	1.902	66/68

Unadjusted q_1^* from study = not calculated (see text)

Human $q_1^* = 0.21\ (mg/kg/day)^{-1}$

6.3.2. Inhalation. Data regarding the carcinogenicity of inhaled dinitrotoluene could not be located in the available literature and EPA has not undertaken route to route extrapolation of carcinogenic response. Thus, an inhalation risk assessment is not presently available.

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APPENDIX

Summary Table for 2,4-Dinitrotoluene*

Route	Species	Experimental Exposure/Dose	Effect	q_1* Cancer Potency Slope $(mg/kg/day)^{-1}$
Oral	rat	15, 100 and 700 ppm in diet for 104 weeks (14 and 95 mg/kg/day)	hepatocellular tumors; mammary benign and malignant tumors	0.68

*Source: Ellis et al., 1979